CME Article
Contraindicated Antiretroviral Drug Combinations

Abe Macher, MD; David Thomas, MD, JD; and Sindy M. Paul, MD, MPH

The proper implementation of combination antiretroviral treatment regimens is fundamental to successful therapeutic outcomes for patients with HIV/AIDS. Unfortunately, some patients are still being prescribed contraindicated antiretroviral regimens that include: 1. stavudine plus zidovudine; 2. Invirase plus two nucleoside analog reverse transcriptase inhibitors (NRTIs); 3. zalcitabine plus didanosine; 4. zalcitabine plus stavudine; and, 5. zalcitabine plus lamivudine. Inappropriate regimens such as these either have limited effectiveness or potential severe toxicity.

Learning Objectives

I. To describe five contraindicated antiretroviral regimens.
II. To understand the pharmacology of contraindicated antiretroviral regimens.
III. To understand where to obtain information about the most recent national recommendations for the treatment of HIV–AIDS.

New Jersey has a high-prevalence of HIV disease. Between July 2000 and June 2001, New Jersey reported 1,857 newly diagnosed cases of AIDS to the Centers for Disease Control and Prevention (CDC). New Jersey ranks fifth in the nation in cumulative reported AIDS cases, and, third in cumulative reported pediatric AIDS cases. Through December 31, 2001, the New Jersey Department of Health and Senior Services' data indicated that 30,535 persons were living with HIV-infection or AIDS in New Jersey.[1]

In July 2002, the International AIDS Society noted that progress in antiretroviral therapy has resulted in achievements as well as in new challenges. The partial restoration of CD4 and CD8 T-cell number and function during suppression of HIV replication with potent antiretroviral therapy has resulted in dramatic reductions in morbidity, mortality, and use of the health care system. However, the toxicity of many current regimens, suboptimal activity and tolerability, and the emergence of drug resistance all point to the need for treatment strategies to address these challenges.[2]

The proper implementation of combination antiretroviral treatment regimens is fundamental to

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successful therapeutic outcomes. Our reviews of medical charts and communications with nurses, physicians, and pharmacists since January 2002, has made us aware that some patients are still being prescribed contraindicated antiretroviral regimens that include: 1. stavudine plus zidovudine; 2. Invirase plus two nucleoside analog reverse transcriptase inhibitors (NRTIs); 3. zalcitabine plus didanosine; 4. zalcitabine plus stavudine; and 5. zalcitabine plus lamivudine.

Stavudine plus Zidovudine

Zidovudine and stavudine are both thymidine analogs; both drugs require intracellular phosphorylation by the cellular enzyme thymidine kinase.[3] As a result of the higher affinity for this enzyme by zidovudine compared to stavudine, it has been suggested that concomitant administration of these two drugs could result in antagonism. Although the *in vitro* data for antagonism between stavudine and zidovudine were conflicting,[3] Havlir and colleagues demonstrated that these drugs, when administered to patients in combination, resulted in limited reduction in levels of plasma HIV RNA, which suggested an *in vivo* antagonism between stavudine and zidovudine. In addition, an evaluation of intracellular stavudine-triphosphate was consistent with antagonism between stavudine and zidovudine.[3]

Consequently, the U.S. Department of Health and Human Services' (DHHS) "Guidelines for Using Antiretroviral Agents among HIV-Infected Adults and Adolescents" recommends that the concurrent administration of stavudine with zidovudine be considered contraindicated for the treatment of HIV disease.[4] The package insert for zidovudine states that "concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated *in vitro*."[5] The package insert for stavudine states that "zidovudine may competitively inhibit the intracellular phosphorylation of stavudine. Therefore, use of zidovudine in combination with stavudine is not recommended."[6]

Invirase plus Two NRTIs

In December 1995, the protease inhibitor saquinavir was released as a hard gelatin capsule formulation named Invirase. Unfortunately, its major drawback was its limited bioavailability caused by incomplete absorption and extensive first-pass metabolism. The poor bioavailability was such a critical factor that the manufacturer of saquinavir reformulated the preparation. Fortovase, the soft gelatin capsule formulation of saquinavir (with a ten-fold greater bioavailability), became available in November 1997.

A clinical trial (NV 15355) compared the efficacy of Invirase with that of Fortovase, each in combination with two NRTIs. At 48 weeks, 57% of the Fortovase recipients had undetectable HIV RNA viral load levels below 400 copies; however, only 38% of the Invirase recipients had undetectable viral load levels.[7] Therefore, the package insert for Invirase states, in a prominent black box warning, that "Invirase (saquinavir mesylate) capsules and Fortovase (saquinavir) soft gelatin capsules are *not* bioequivalent and cannot be used interchangeably. When using saquinavir as part of an antiviral regimen, Fortovase is the recommended formulation. Invirase may be considered if it is to be combined with antiretrovirals that significantly inhibit saquinavir's metabolism."[8]

Zalcitabine plus Didanosine, and Zalcitabine plus Stavudine

Peripheral neuropathy is the major clinical toxicity of zalcitabine. It was noted in 17%–31% of patients in the initial trials. The frequency of stavudine-associated peripheral neuropathy is 5%–24% and of didanosine-associated peripheral neuropathy, 5%–12%. The clinical features of zalcitabine-associated toxicity include bilateral sensorimotor neuropathy with numbness and burning in distal extremities, usually after 2–6 months of therapy, followed by shooting or continuous pain. Symptoms usually resolve slowly if the drug is promptly discontinued. However, with contin-

ued use, the peripheral neuropathy may be irreversible and require narcotics.[9] Because of overlapping neurotoxicity, clinicians should avoid the concurrent administration of zalcitabine with didanosine, and zalcitabine with stavudine.[4]

The package insert for zalcitabine states that "the concomitant use of zalcitabine with drugs that have the potential to cause peripheral neuropathy should be avoided."[10]

Zalcitabine plus Lamivudine

Zalcitabine and lamivudine are cytidine analogs that require intracellular metabolism to their active triphosphate forms in order to inhibit viral reverse transcriptase and cause proviral DNA chain termination in target lymphocytes. The initial steps in the phosphorylation of both zalcitabine and lamivudine are carried out by the enzyme deoxycytidine kinase. When administered together, the two drugs are in direct competition for the catalytic site of this enzyme in HIV-infected lymphocytes.[11] *In vitro* studies by Veal demonstrated that lamivudine inhibits zalcitabine phosphorylation.[12] Therefore, it is recommended that zalcitabine should not be co-administered with lamivudine.[4, 13]

Conclusion

It is imperative that antiretroviral drug combinations are carefully chosen to obtain maximum benefits from each individual agent. Inappropriate regimens, such as those described above, either have limited effectiveness or potential severe toxicity. It is incumbent upon all health care providers to control HIV disease as effectively as possible and to be cognizant of their unique opportunity to have an impact on the HIV pandemic. We recommend that clinicians and pharmacists refer to the DHHS's antiretroviral treatment guidelines, which are regularly updated and readily available on the Internet at http://www.hivatis.org. In addition, a free continuing-medical-education lecture, funded by the New Jersey Department of Health and Senior Services, on diagnosis and management of HIV disease is available through the New Jersey Academy of Medicine. *NJM*

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"Contraindicated Antiretroviral Drug Combinations"

1. Stavudine and zidovudine should not be administered concomitantly because they:
   A. Affect different phases of HIV replication
   B. Are non-nucleoside reverse transcriptase inhibitors
   C. Exhibit pharmacologic antagonism by competing for the same enzyme
   D. Oncrease the risk of peripheral neuropathy

2. When used with two nucleoside analog reverse transcriptase inhibitors, Invirase should not be administered without ritonavir because:
   A. Invirase is a nucleoside analog reverse transcriptase inhibitor
   B. Invirase is poorly bioavailable
   C. Invirase is a non-nucleoside reverse transcriptase inhibitor
   D. Of the risk of peripheral neuropathy

3. Zalcitabine and didanosine should not be administered concomitantly because they:
   A. Affect different phases of HIV replication
   B. Are both cytidine analogs
   C. Exhibit pharmacologic antagonism
   D. Increase the risk of peripheral neuropathy

4. Zalcitabine and lamivudine should not be administered concomitantly because they:
   A. Are both non-nucleoside reverse transcriptase inhibitors
   B. Exhibit pharmacologic antagonism by competing for the same enzyme
   C. Are both protease inhibitors
   D. Increase the risk of peripheral neuropathy

5. Which of the following antiretroviral combinations is contraindicated for the treatment of HIV disease?
   A. Fortovase plus 2 nucleoside analog reverse transcriptase inhibitors
   B. Zalcitabine plus stavudine
   C. Zalcitabine plus zidovudine
   D. Zidovudine plus lamivudine

Answer Sheet

"Contraindicated Antiretroviral Drug Combinations"

Darken the correct answers

1. [A] [B] [C] [D] 2. [A] [B] [C] [D] 3. [A] [B] [C] [D]
4. [A] [B] [C] [D] 5. [A] [B] [C] [D]

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